LISTING OF THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

1. (**Currently Amended**) A method for generating a secondary library of protein sequences **with at least one desired characteristic relative to** [[of]] a target protein comprising:

a) inputting the coordinates of said target protein into a computer;

b) selecting a plurality of variant positions based upon said at least one desired characteristic to generate a set of primary variant positions;

c) utilizing said coordinates**, said set of primary variant positions** and a forcefield calculation to generate a primary library of primary protein sequences comprising a plurality of primary variant amino acid residues at **said** primary variant positions;

[[c]]**d**) generating a probability distribution of amino acid residues in a plurality of variant positions from said force field calculation;

[[d]]**e**) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences; wherein at least one of said secondary protein sequences is different from said primary protein sequences; and

[[e]]**f**) synthesizing **and screening for said at least on desired characteristic** a plurality of said secondary protein sequences.

2. (**Currently Amended**) A method for generating a secondary library of protein sequences **with at least one desired characteristic relative to** [[of]] a target protein comprising:

a) inputting the coordinates of said target protein into a computer;

b) selecting a plurality of variant positions based upon said at least one desired characteristic to generate a set of primary variant positions;

c) utilizing said coordinates**, said set of primary variant positions** and a forcefield calculation to generate a primary library of primary protein sequences comprising a plurality of primary variant amino acid residues at **said** primary variant positions;

[[c]]**d**) generating a probability distribution of amino acid residues in a plurality of variant positions from said force field calculation;

[[d]]**e**) generating a set of oligonucleotide probes each encoding at least one of said primary variant amino acid residues;

[[e]]**f**) using said probes in a polymerase chain reaction (PCR) to generate a plurality of oligonucleotide sequences, each encoding a plurality of secondary variant protein sequences, wherein at least one of said secondary variant protein sequences is different from said primary protein sequences; and,

[[f]]**g**) producing **and screening for said at least on desired characteristic** said secondary variant protein sequences in host cells transformed with said oligonucleotide sequences.

3. (Previously Presented) A method according to claim 2 wherein said PCR is multiple PCR and wherein

said probes are pooled.

4. (Previously Presented) A method according to claim 3 wherein said probes are added in equimolar amounts.

5. (Previously Presented) A method according to claim 3 wherein said probes are combined in amounts that correspond to the probability of said variant amino acid residues in said probability distribution table.

6. (Cancelled)

7. (Previously Presented) A method according to claim 1 wherein said target protein is an enzyme.

8. (Previously Presented) A method according to claim 1 wherein said target protein is a therapeutic protein.

9. (Previously Presented) A method according to claim 1 wherein the coordinates of a region surrounding a binding site to a receptor is input into a computer.

10. (Previously Presented) A method according to claim 1 wherein said primary variant positions comprise a region surrounding a binding site.

11. (Previously Presented) A method according to claim 8 wherein said primary variant positions comprise a region surrounding a binding site to a receptor.

12. (Previously Presented) A method according to claim 7 wherein said primary variant positions comprise a region surrounding the active site of said enzyme.

13. (Previously Presented) A method according to claim 7 wherein said primary variant positions comprise a region surrounding the catalytic residues of said enzyme.

14. (**Currently Amended**) A method for generating a secondary library of protein sequences **with at least one desired characteristic relative to** [[of]] a target protein comprising:

(a) generating a primary library comprising:

(i) inputting the coordinates of a target protein with variable residue positions;

(ii) selecting a plurality of variable residue positions based upon said at least one desired characteristic to generate a set of primary variant positions;

(iii) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue position comprises at least two different amino acid side chains; and

[[(iii)]]**(iv)** analyzing the interaction of each of said amino acids with plurality of said amino acids at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences;

(b) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences;

(c) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants; and

(d) synthesizing **and screening for said at least on desired characteristic** a plurality of said secondary

3

protein sequences;

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation

15. (**Currently Amended**) A method for generating a secondary library of protein sequences **with at least one desired characteristic relative to** [[of]] a target protein comprising:

(a) generating a primary library comprising:

(i)   inputting the coordinates of a target protein ~~with variable residue positions~~;

(ii)   selecting a plurality of variable residue positions based upon said at least one desired characteristic to generate a set of primary variant positions;

(iii)   establishing a group of potential rotamers for each of said variable residue positions, wherein the group of potential rotamers for at least one of said variable residue position has a rotamer selected from each of at least two different amino acid side chains; and

[[(iii)]]**(iv)**   analyzing the interaction of each of said rotamers with plurality of said rotamers at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences;

(b) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences;

(c) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants; and,

(d) synthesizing **and screening for said at least on desired characteristic** a plurality of said secondary protein sequences,

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

16. (Previously Presented) A method according to claim 14, wherein said force field calculation is Self-Consistent Mean Field (SCMF).

17. (**Currently Amended**) A method for generating a secondary library of protein variants **with at least one desired characteristic relative to** [[of]] a target protein comprising:

(a) generating a primary library comprising:

(i)   inputting the coordinates of a target protein ~~with variable residue positions~~;

(ii)   selecting a plurality of variable residue positions based upon said at least one desired characteristic to generate a set of primary variant positions;

(iii)   establishing a group of potential rotamers for each of said variable residue positions, wherein the group of potential rotamers for at least one of said variable residue position has a rotamer selected from each of at least two different amino acid side chains; and

[[(iii)]]**(iv)**   analyzing the interaction of each of said rotamers with plurality of said rotamers at a plurality of variable residue positions and all or part of the remainder of said protein to generate a

4

primary library of primary sequences optimized for at least one scoring function;

(b) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences;

(c) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants; and,

(d) synthesizing **and screening for said at least on desired characteristic** a plurality of said secondary protein sequences,

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

18. (Previously Presented) A method according to claim 17, wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

19. (Previously Presented) A method according to claim 14, 15, or 17, wherein said analyzing step utilizes a force field calculation.

20. (Previously Presented) A method according to claim 14, 15, or 17, wherein said generating step (B) utilizes a force field calculation.

21. (Previously Presented) A method according to claim 14, 15, or 17, wherein said combining step utilizes a force field calculation.

22. (**Currently Amended**) A method for generating a secondary library of protein sequences **with at least one desired characteristic relative to** [[of]] a target protein comprising:

a) inputting the coordinates of said target protein into a computer;

b) specifying a list of at least two primary variant positions **based upon said at least one desired characteristic**;

c) utilizing said coordinates and a forcefield calculation to generate a primary library comprising a plurality of primary variant amino acid residues at said primary variant positions;

d) generating a probability distribution of amino acid residues in a plurality of variant positions from a force field calculation;

e) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences; wherein at least one of said secondary protein sequences is different from said primary protein sequences; and,

f) synthesizing **and screening for said at least on desired characteristic** a plurality of said secondary protein sequences.

23. (Previously Presented) A method according to claim 22 wherein said primary library is generated using a monte carlo search.

24. (Previously Presented) A method according to claim 22 wherein said primary library is generated

using a genetic algorithm.

25. (Previously Presented) A method according to claim 22 wherein said probability distribution table is derived from frequencies of occurrence in a primary variant library.

26. (Previously Presented) A method according to claim 1 wherein combining said plurality of said amino acid residues from said probability distribution comprises a calculation in said computer.